

CLAIMS

We claim:

1. A method for isolating compounds that possess amyloid inhibitory activity from plant matter of the genus *Uncaria*, the method comprising the steps:

5        a) preparing a polar solvent extract of *Uncaria* plant matter, where the polar solvent extraction is selected from one of the extraction methods from the group of extraction methods consisting of extraction with water, extraction with a water solution of a polar alcohol, extraction with a water solution of acetonitrile and extraction with a water solution of another polar organic solvent selected from the group of polar organic solvents consisting of triethanolamine, acetone, and the like, and running the extract through a first column that comprises hydroxy group containing resin, resin having hydrophobic characteristics but without any hydroxy groups, or a mixture of both;

10      b) eluting the first column with distilled water, followed by eluting with not more than 2-4 column bed volume washings with a dilute polar alcohol/water solution having an alcohol/water ratio not greater than 50/50, and discarding any eluate;

15      c) eluting the first column with one or more column bed volume washings of a polar alcohol/water solution having an alcohol/water ratio between 50/50 and substantially pure alcohol, and collecting and drying the eluted volumes to a dried material.

20      2. The method of claim 1 wherein the column that comprises hydroxy containing resin, resin having hydrophobic characteristics but without any hydroxy groups, or a mixture of both is a column selected from the group of columns consisting of C2

column, C4 column, C18 column, and the like carbon-containing columns, Tris-acrylate column, LH-20 column, Affi-prep 10 gel column, and the like.

3. The method of claim 1 wherein the polar alcohol/water solution has an alcohol/water ratio of 75/25 or higher.
- 5 4. The method of claim 1 wherein the washing in step (c) is effected with substantially pure methanol.
5. The method of claim 1 wherein the plant matter of the genus *Uncaria* is taken from one or more of the plants of the various *Uncaria* species plant group consisting of *tomentosa*, *attenuata*, *elliptica*, *guianensis*, *pteropoda*, *bernaysli*, *ferra DC*,  
10 *kawakamii*, *rhyncophylla*, *calophylla*, *gambir*, and *orientalis*.
6. The method of claim 1 wherein the plant matter of the genus *Uncaria* is taken from *Uncaria tomentosa*.
7. The method of claim 6 wherein the *Uncaria tomentosa* plant matter is taken from one or more of the group of plant parts consisting of inner bark and root.
- 15 8. The method of claim 1 further comprising the steps:
  - d) applying an aqueous solution of the dried material from step (c) to a second column comprising a hydrophobic resin, the second column having been preparatorily equilibrated in a solvent comprising about 95% water/5% acetonitrile, referred to herein as solvent A, and then eluting the second column with more solvent A and discarding the eluate;
  - e) eluting the second column with a mixture of solvent A containing 10-15% of a solvent comprising about 95% acetonitrile/5% water, referred to herein as solvent B, and collecting and drying the eluted volumes to a dried material.
- 20 9. The method of claim 8 wherein the second column comprising a hydrophobic resin is a column selected from the group of columns consisting of C18 SPE, Varian Chroma..Zone™, other HPLC columns, other carbon-containing columns, and the like.

10. The method of claim 1 or 8 further comprising the steps:

5           f) making one or more injections of a solution of the dried material of step (c) or the dried material of step (e) in a solvent selected from the group of solvents consisting of water, water/dilute alcohol and solvent A comprising no more than 10% solvent B, into an HPLC instrument having a diode array uv/vis detector with a graphic display, the HPLC instrument further comprising a reverse-phase column;

10           g) eluting the material through the HPLC column using a solvent gradient profile as follows: 10% solvent B for about the first 20 minutes from start of elution, 10 to 100% solvent B gradient for about minutes 20 to 30 from start of elution, and 100 to 10% solvent B gradient for about minutes 30 to 32 from start of elution, while observing the uv/vis detector graphic display during the elution gradient over time, and separating fractions of the eluate at elution times corresponding to times associated with the graphic display peaks.

15. 11. The method of claim 10, wherein the reverse-phase column has dimensions of about 2.2cm X 25cm and contain about 95ml of C18 reverse phase resin, wherein the solution of the dried material is a solution of about 50 mg of the dried material of step (c) in about 1-2 ml of solvent A, wherein the step of injecting the solution of dried material into the HPLC may be repeated, wherein a HPLC column solution gradient 20 flow rate is set to about 5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions F though N of the eluate are collected at the following times: fraction G (13-14 minutes), fraction F (15-16 minutes), fraction H (17-20 minutes), fraction I (21 25 minutes), fraction J (22 - 23 minutes), fraction K1 (24 minutes), fraction K2 (25

minutes), fraction L (26-27 minutes), fraction M (27-28 minutes), and fraction N (28-29 minutes).

12. The method of claim 10, wherein the reverse-phase column with dimensions of 1.0 cm X 25.0 cm containing 20ml of C18 reverse phase resin, wherein the solution of 5 the dried material of step (c) is a solution of 50 µg of the dried material in 50-100µl of solvent A, wherein the step of injecting the solution into the HPLC is repeated multiple times, wherein a HPLC column solution gradient flow rate is set to about 1.5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 10 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions F though O of the eluate are collected at the following times: fraction G (12-13 minutes), fraction F (13-14 minutes), fraction H (15 minutes), fraction I (16 minutes), fraction J (18-19 minutes), fraction K1 (20 minutes), fraction K2 (21 minutes), fraction L (21-23 minutes), fraction M (23 minutes), fraction N (24 minutes), and fraction O (26-27 15 minutes).

13. The method of claim 10 wherein steps (f) and (g) are as follows:

f) injecting a solution of 1 gram of the dried material of step (c) in 5 - 10 ml of solvent A into an HPLC instrument having a Varian model 320 uv-vis detector set at 230 nm with a graphic display, the HPLC further comprising a 20 4.14 cm X 25 cm Varian Dynamax column further comprising 380 ml of C-18 reverse phase resin, the column fitted to a Varian Prostar 215 solvent delivery system, or the like.

g) eluting the HPLC column at a solution gradient flow rate of about 50 ml/minute, and further wherein the solvent gradient profile is with a solvent 25 C/solvent D gradient as follows: 0-4 minutes, 25% D; 4-11 minutes, 25-30% D gradient; 11-14 minutes, 30-90% D gradient; 14-17 minutes, 90% D; and 17-19

minutes, 90-25% D gradient, where C is water and D is methanol, such that fractions F through O of the eluate are separated at elution times corresponding to times associated with the graphic display peaks.

14. The method of claim 1 wherein the preparation in step (a) of the extract of  
5 *Uncaria* is as follows:

- 1) adding 4000ml of methanol to 1 kg of *Uncaria tomentosa* and mixing
- 2) centrifuging the mixture at X2,500g using a centrifuge for 30 minutes and collecting the supernatant;
- 3) extracting the insoluble material about 3 more times as steps a and b above;
- 10 4) combining the supernatants and evaporating to a dried extract, or to at least about 500 ml volume, using a rotary evaporator at 50°C;
- 5) washing the dried extract, or the 500ml volume, 4 times with 300ml of petroleum ether, and discarding the ether layer;
- 15 6) further evaporating any remaining methanol to dryness using a rotary evaporator at 50°C;
- 7) extracting the dried extract 5 times with 150ml of distilled water, followed by centrifugation at 2,500Xg for 30 minutes each time, and
- 8) combining the supernatants and then lyophilizing using a freeze-dryer.

15. The method of claim 14 wherein the further preparation of the extract of  
20 *Uncaria* from the resulting lyophilized extract includes the following additional steps:  
9) dissolving the resulting lyophilized extract into about 500 ml of distilled water, and applying 50-100ml portions to a 400 ml LH-20 column equilibrated with distilled water.  
25 10) eluting the LH-20 column with 1,100ml of distilled water (~3 column volumes) and discarding the amber/yellow, non-active fractions;

11) eluting the LH-20 column with 1,100ml of 100% methanol (~3 column volumes) and collecting a set of active fractions and evaporating to dryness using a rotary evaporator at 50°C.

16. The method of claim 8 wherein the aqueous solution of a dried material from step (c) is further prepared by the following steps:

1) dissolving the dried material in water at 80 mg/ml and applying 5 ml at a time to a disposable C18 SPE column (10 gram) equilibrated in a first solvent comprising about 95% water/5% acetonitrile/ 0.1% TFA;

2) washing with 3 column bed volumes of the first solvent and discarding the eluate.

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3) eluting with 3 column bed volumes of the first solvent further comprising about 12.5% of a second solvent comprising about 95% acetonitrile/5% water/0.1% TFA, and

4) lyophilizing the corresponding fractions using a freeze-dryer.

15 17. The method of claim 8 wherein the aqueous solution of a dried material from  
step (c) is further prepared by the following steps:

1) dissolving the lyophilized fractions at 5 grams in 20 ml water and applying 20ml at a time to a Varian Chroma.Zone™ apparatus

2) washing with 3 column bed volumes of a first solvent comprising about 95% water/5% acetonitrile/ 0.1% TFA and discarding the eluate;

3) eluting with 3 column bed volumes of the first solvent further comprising about 12.5% of a second solvent comprising about 95% acetonitrile/5% water/0.1% TFA, and

4) collecting and drying the next 3 column bed volumes of eluate

- a) adding 4000ml of methanol to 1 kg of *Uncaria tomentosa* and mixing
- b) centrifuging the mixture at X2,500g using a centrifuge for 30 minutes and collecting the supernatant;
- c) extracting the insoluble material about 3 more times as steps a and b above;
- d) combining the supernatants and evaporating to dryness (or until about 500 ml volume is reached) using a rotary evaporator at 50°C,
- e) taking the powdered extract (or about 500ml volume), washing 4 times with 300ml of petroleum ether, and discarding the ether layer,
- f) evaporating the methanol to dryness using a rotary evaporator at 50°C;
- g) extracting the solid material 5 times with 150ml of distilled water, followed by centrifugation at 2,500Xg for 30 minutes each time;
- h) combining the supernatants and then lyophilizing using a freeze-dryer;
- i) dissolving the resulting lyophilized extract into about 500 ml of distilled water, and applying 50-100ml portions to a 400 ml LH-20 column equilibrated with distilled water.
- j) eluting the LH-20 column with 1,100ml of distilled water (~3 column volumes) and discarding the amber/yellow, non-active fractions;
- k) eluting the LH-20 column with 1,100ml of 100% methanol (~3 column volumes) and collecting a set of active fractions and evaporating to dryness using a rotary evaporator at 50°C;
- l) dissolving the fractions of step k in water (80mg/ml) and applying 5 ml at a time to a 10gm disposable C18 SPE column equilibrated in solvent A (solvent A is 95% water/5% acetonitrile/0.1% TFA);
- m) washing the column with 3 volumes of solvent A and discarding the eluate;
- n) eluting the column with 3 volumes of solvent A containing 12.5% solvent B (solvent B is 95% acetonitrile/5% water/0.1% TFA) and lyophilizing the eluate;

o) taking 50mg of the lyophilized eluate of step n and injecting multiple times into a Hewlett-Packard 1100 Series HPLC instrument with diode array detector, fitted with a 2.2cm X 25 cm Vydac 218TP1022 C18 reverse-phase column maintained at 25°C and at a flow rate of 5 ml/min;

5 p) eluting the sample with the following solvent profile, 10% B for 0 to 20 minutes, 10 -100 % B gradient for minutes 20 to 30, and 100-10% B gradient for minutes 30-31, where B is 95% acetonitrile/5% water/0.1% TFA;

10 q) and separating and collecting the fractions into 11 major components defined as fraction G (13-14 minutes), fraction F (15-16 minutes), fraction H (17-20 minutes), fraction I (21 minutes), fraction J (22 - 23 minutes), fraction K<sub>1</sub> (24 minutes), fraction K<sub>2</sub> (25 minutes), fraction L (26-27 minutes), fraction M (27-28 minutes), and fraction N (28-29 minutes).

II 19. A composition further referred to herein as PTI-777 made according to the process of claims 1, 8, 10-13 or 18. <sup>11-13</sup> which fraction is PTI-777?

15 III 20. A composition further referred to herein as a PTI-777 fraction, the fraction selected from the group of fractions consisting of PTI-777 fraction G, PTI-777 fraction F, PTI-777 fraction H, PTI-777 fraction I, PTI-777 fraction J, PTI-777 fraction K<sub>1</sub>, PTI-777 fraction K<sub>2</sub>, PTI-777 fraction L, PTI-777 fraction M, PTI-777 fraction N, and PTI-777 fraction O, wherein the selected fraction is made according to the process of any 20 of the claims 1, 8, 10-13.

IV 21. The composition of claim 20 wherein the PTI-777 fraction selected from the group of fractions is PTI-777 fraction H.

I 22. The method of claim 1 further comprising the steps:  
25 d) applying an aqueous solution of the dried material from step (c) to a second column, LH-20 or the like, eluting the material from the column with successive column volumes of water/methanol mixtures containing 0.1% TFA,

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24. A method of treatment, prevention or management of an amyloidosis, or a disease related to alpha-synuclein, in a mammalian subject susceptible to, or afflicted by, the amyloidosis or alpha-synuclein disease, the method comprising the step of administering to the subject a therapeutic amount of <sup>L413</sup> [the composition of claim 12] and/or claim 23.

25. A method of treatment, prevention or management of an amyloidosis, or a disease related to alpha-synuclein, in a mammalian subject susceptible to, or afflicted by, the amyloidosis or alpha-synuclein disease, the method comprising the step of administering to the subject a therapeutic amount of fraction G, fraction F, fraction H, fraction I, fraction J, fraction K<sub>1</sub>, fraction K<sub>2</sub>, fraction L, fraction M, fraction N and/or fraction O <sup>L413</sup> [compositions] of claim 20.

26. The method of claim 24 wherein the amyloidosis has an associated amyloid and the amyloidosis is selected from the group of amyloidoses associated with Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis associated with type II diabetes, the amyloidosis associated with chronic inflammation, various forms of malignancy and Familial Mediterranean Fever, the amyloidosis associated with multiple myeloma and other B-cell dyscrasias, the amyloidosis associated with the prion diseases including Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru and animal scrapie, the amyloidosis associated with long-term hemodialysis and carpal tunnel syndrome, the amyloidosis associated with endocrine tumors such as medullary carcinoma of the thyroid, and the alpha-synuclein associated diseases including Parkinson's disease and Lewy body disease.

27. The method of claim 24 wherein the amyloidosis is associated with Alzheimer's disease.

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28. The method of claim 26 wherein the associated amyloid is beta-amyloid protein or A $\beta$ , AA amyloid or inflammation-associated amyloid, AL amyloid, amylin or islet amyloid polypeptide, PrP amyloid, beta $_2$ -microglobulin amyloid, transthyretin or prealbumin, or variants of procalcitonin.

5 29. A method for the treatment, inhibition, prevention or management of amyloid fibril or alpha-synuclein fibril formation, deposition, accumulation, aggregation and/or persistence in a mammalian subject, the method comprising the step of administering to the subject a therapeutic amount of the composition of claims 19, 20 or 23.

30. The method of claim 29 wherein the route of administration of the method of treatment is selected from the group consisting of oral administration, parenteral injection, intraperitoneal injection, intravenous injection, subcutaneous injection, or aerosol spray administration.

10 31. A pharmaceutical agent comprising a therapeutically effective amount of a material made according to the process of claims 1, 8, 10-13, 18 or 22, the therapeutic amount of the material selected for efficacy in treating an amyloid disease in a patient.)

15 32. A pharmaceutical agent comprising a therapeutically effective amount of a compound selected from the group consisting of chlorogenic acid and epicatechin, the compound and the therapeutic amount of the compound selected for efficacy in treating an amyloid disease in a patient.)

20 33. The pharmaceutical agent of claim 31 or 32 wherein the therapeutically effective amount of a material comprises a dosage in the range of from about 10 to 1,000 mg/kg of body weight of the patient.  
*LAB for chm 32*

25 34. The pharmaceutical agent of claim 33 wherein the therapeutically effective amount of a material comprises a dosage in the range of from about 10 to 100 mg/kg of body weight of the patient.

35. The pharmacological agent of claim 33 wherein said amyloid disease for treatment is selected from the group of amyloid diseases associated with Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis associated with type II diabetes, the amyloidosis associated with chronic inflammation, various forms of malignancy and Familial Mediterranean Fever, the amyloidosis associated with multiple myeloma and other B-cell dyscrasias, the amyloidosis associated with the prion diseases including Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru and animal scrapie, the amyloidosis associated with long-term hemodialysis and carpal tunnel syndrome, the amyloidosis associated with endocrine tumors such as medullary carcinoma of the thyroid, and the alpha-synuclein associated diseases including Parkinson's disease and Lewy body disease.

Lewy body disease.

36. The pharmacological agent of claim 35 wherein said amyloid disease for treatment is Alzheimer's disease.

15 treatment is Alzheimer's disease.  
37. The pharmaceutical agent of claim 33 further comprising a pharmaceutically  
acceptable carrier, diluent, or excipient.

38. The pharmacological agent of claim 33 wherein the therapeutically effective amount of the material has an amyloid inhibitory activity or efficacy greater than 50%.

38. The pharmacological agent of claim 33 wherein the therapeutically effective amount of the material has an amyloid inhibitory activity or efficacy greater than 50%.